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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,455	08/29/2005	Benjamin Simon Pickard	9013-63	2347

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
12/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,455	PICKARD ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-41 and 46-55* is/are pending in the application.

4a) Of the above claim(s) *49-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-41 and 46-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 38-41 and 46-55 are pending.

Claims 49-55 are withdrawn from examination as detailed in the previous Office Action.

Claims 38-41, and 46-48 are examined on the merits.

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 09/17/2008.

Applicants' Declaration, remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. No new grounds of rejection are presented in this Office Action. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL.**

Declaration Under 37 CFR 1.132

1. The Declaration under 37 CFR 1.132 filed 09/17/2008 has been considered but is insufficient to overcome the rejection of claims 38-41 and 46-55 under 35 USC 112 1st ¶ for lack of enablement, as set forth in the last Office action. The Declaration in view of the rejection is discussed in the relevant response to the remarks later in this Office Action.

Withdrawn Objection to the Specification - Sequence Compliance

2. The objection to the specification for compliance to the Sequence Rules is **WITHDRAWN** in light of the amendments to the specification to identify sequences contained in the specification using the SEQ ID NOs from the sequence listing.

Withdrawn Objection - Drawings

3. The drawings were received on 09/17/2008. These drawings are acceptable. The objection to the drawings as set forth in the previous Office Action is **WITHDRAWN** in light of the new drawings.

Withdrawn Objection to the Specification

4. The objection to the specification for the recitation of browser executable code is **WITHDRAWN** in light of the amendments to the specification. The disclosure is objected to because of the following informalities:

Maintained Objection to the Specification

5. The disclosure is objected to because of the following informalities:

Page 35 of the specification recites the term 'comorbin schizophrenia', where likely the phrase 'comorbid schizophrenia' is intended.

Appropriate correction is required.

Withdraw Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

6. The rejection of claims 38-41 and 46-48 under 35 U.S.C. 112, second paragraph, as set forth in the previous Office Action, is **WITHDRAWN** in light of the amendments to the claims to require that determination of a mutation is indicative of susceptibility to schizophrenia and/or affective psychosis.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 38-41 and 46-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

Claims 38-41 and 46-48 are drawn to a method of identifying a human subject as having susceptibility to schizophrenia and/or affective psychosis. The claimed methods requiring determining if the GRIK4 gene in an individual is disrupted.

The claims encompass methods for determining disruption by detecting mRNA level (claim 39), detecting gene product by immunological techniques (claims 40 and 41), and nucleic acid hybridization techniques (claims 46-48).

The claims encompass the determination of any mutation or chromosomal rearrangement.

The nature of the invention thus requires knowledge of a correlation between any mutation of chromosomal rearrangement that disrupts the GRIK4 gene and the presence of or susceptibility to schizophrenia and/or affective psychosis.

Direction provided by the specification and working example

The instant specification (p.17) asserts that the presence of or susceptibility to schizophrenia and/or affective psychosis may be determined by determining if GRIK4 has been disrupted in an individual. The specification provides, relevant to the analysis of the GRIK4 gene, an example (p.33 – Example 3) of a single particular patient (i.e. patient 2). The specification indicates that patient 2 suffered from chronic schizophrenia, and had complex chromosome abnormalities (p.34). The specification teaches analysis of a particular chromosome breakpoints on chromosomes 2 and 11, and the detection of an 11q23.3 breakpoint using cosmid FISH.

The instant specification does not provide any guidance or examples regarding relative mRNA levels as indicative of any particular chromosome rearrangement.

The instant specification does not provide any guidance or examples regarding immunological methods to detect a gene product that is indicative of any particular chromosome rearrangement.

The instant specification provides only an example of a single human subject, and does not provide any validation of the proposed correlation between a chromosomal rearrangement and schizophrenia by analysis of any family pedigrees or any other separate populations in which the association is confirmed.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to making determining if a particular gene sequence has an alteration is high, the level of unpredictability in correlating any detected nucleic acid sequence mutation with a

particular diagnosis, such as schizophrenia or any affective psychosis, is higher. Such unpredictability is demonstrated by the prior art and the post-filing art.

Because the claims encompass determining if GRIK4 has been disrupted by detecting relative level of mRNA expressed by the gene, or detecting GRIK4 gene products by an immunological techniques, while the specification teaches only detection of GRIK4 mutations using sequence specific hybridization, it is relevant to point out the unpredictability in detecting a gene mutation using relative level of mRNA expressed by the gene or immunological techniques. Regarding relative mRNA levels, Orntoft et al (2002) teaches that mRNA expression and gene copy alteration are unpredictably discordant (Table I; p.40 left col.). It is thus unpredictable, given the lack of any evidence in the instant specification, as to what level of GRIK4 mRNA expression, as compared to any particular standard control, would be indicative of any GRIK4 disruption. Additionally, the claims encompass analyzing the level of GRIK4 gene product using immunological techniques, however the post-filing art of Chan teaches that cells have elaborate regulatory mechanisms at the level of transcription, post-transcription, and post-translation (p.1, last paragraph), and that transcript and protein abundance measurements may not be concordant (p.3, sixth full paragraph). Thus it is unpredictable as to whether or not any detection of GRIK4 gene product level would be indicative of the particular disruption that is taught in the instant specification.

Furthermore, while the claims encompass any GRIK4 disruption cause by any mutation or rearrangement (i.e. any amount of nucleotide sequence alteration), it is relevant to point out that the instant specification teaches only a single particular

chromosomal rearrangement. And while the specification hypothesizes (p.35) that reduced GRIK4 gene dosage resulting from GRIK4 disruption is the cause of the schizophrenic phenotype in patient 2, the specification provides no evidence in support of this proposed mechanism. There is no analysis of any functional consequences of the GRIK4 rearrangement. The breadth of mutations encompassed by the broad language of the claims is particularly relevant considering the post-filing art of Li et al and Shibata et al, which indicate a lack of association between GRIK4 SNPs and schizophrenia in Chinese and Japanese populations, respectively.

It is also relevant to point out that the asserted association between GRIK4 mutations and schizophrenia is based on the analysis of a single patient. Lucentini (2004) teaches the general unpredictability in associating a gene or mutation of a gene with a particular phenotype. Lucentini reveals that most gene association studies are typically wrong. Lucentini teaches that it is strikingly common for follow-up studies to find gene-disease associations wrong (left column, 3rd paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (left column, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical methods, should be included in the gene association studies (middle column, 1st complete paragraph). For example, in an anlysis of a translocation involving locus 11q23 (where the GRIK4 gene is at 11q23.3), Baysal et al (2002) teaches that in a family the particular

translocation only partially cosegregates with the bipolar phenotype, with 5 translocation carriers not being affected.

Finally, because the claims encompass associating any GRIK4 mutation with a diagnosis or susceptibility to any affective psychosis, where the specification teaches only the analysis of a single patient with schizophrenia, it is relevant to point out the unpredictability in associating any particular SNP with a particular phenotypic trait. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. One would have to perform large case:control and family studies to determine that the GRIK4 gene is robustly and reliably associated with schizophrenia or any other affective psychosis. Such experimentation would require the analysis of any mutation in the GRIK4 gene. One would also be required to establish that mRNA or gene product levels are indicative of any GRIK4 mutation.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the few specific

working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments (p.13-18 of remarks) and the Declaration of Benjamin Simon Picard have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Initially it is noted that in light of the amendments to the claims the portions of the rejection regarding the analysis of non-human subject organisms has been withdrawn from the rejection as set forth in the instant Office Action.

Applicants have argued that the claimed methods are clear and well defined in their scope (p.14 of Remarks). The Examiner has not, in the instant rejection, raised an issue of the clarity or definition of the scope of the claim. At issue in the rejection is that fact that the breadth of the claims (e.g. requiring the association of any GRIK4 mutation or detected protein level with susceptibility to any affective psychosis) encompasses methods that are inherently unpredictable and not taught in the instant specification or the prior art.

Applicants have further argued (p.14 of Remarks) that the claimed methods are the practical application of Applicants' discovery of a mutation in the GRIK4 gene of a subject with schizophrenia. As set forth in the rejection, the specification teaches only the example of a single patient with a single particular alteration in the GRIK4 gene.

The claims encompass the determination of any mutation in the GRIK4 gene, where as set forth in the rejection there is a high degree of unpredictability in generically associating any gene mutation with a particular phenotype. Thus while the Declaration (part 3) asserts that the skilled artisan would be able to identify a susceptible subject by identification of any one of several possible lesions, it is noted that the claims are in no way limited to any particular molecular lesion; thus the claims require the skilled artisan to possess knowledge of which lesions are predictive of susceptibility. And while the Declaration indicates that the specific translocation of the specification may 'generally reduce the operational quantity of the damaged gene and its messenger RNA (mRNA) leading to the pathological reduction of functional protein', the claims encompass any GRIK4 mutation that may, or may not, result in any level of mRNA and/or protein reduction. The specification does not provide for such breadth of mutations and their effects on mRNA or protein quantity, or what quantities are required for any pathological effect.

And while the Declaration asserts (part 3) that there is a *de facto* link between this gene and mental illness, the Examiner maintains that, in view of the references cited in the rejection, the identification of a single particular alteration in a single patient, as detailed in the instant specification and the cited references, is not convincing evidence that such an association would be reliably identified in any other individual or any population of individuals.

And while the Declaration asserts (part 4) that the post-filing art teaches a common 14 base deletion within GRIK4 that is associated with altered risk for bipolar

disorder, it is noted that this mutation is not specifically disclosed in the specification as originally filed, nor does this assertion indicate that any particular mRNA or protein level would be considered pathological.

Applicants' have argued (p.15 of Remarks) that the artisan of ordinary skill would use the teachings of the instant specification to carry out further correlation studies to identify subject susceptible to schizophrenia and/or affective disorder. The argument is not persuasive. The claims encompass literally any mutations in the GRIK4 gene. The claimed methods are not methods of screening (e.g. methods to determine whether or not a mutation:phenotype association exists), but methods of identification of a subject with a susceptibility to a phenotype (i.e. essentially methods to diagnose a genetic predisposition). The methods require that the artisan practicing the method can a prior determine the required susceptibility based on any determined mutation.

Next Applicants have argued (p.16 of Remarks) that there would not be undue experimentation in practicing the claimed method, and that the skilled artisan would recognize the functional consequences of the described GRIK4 rearrangement. The arguments are not persuasive. As set forth in the rejection, the issue at hand is not the ability for the skilled artisan to recognize a mutation in the GRIK4 gene, the issue is the ability to associate any determined GRIK4 mutation with a predisposition for schizophrenia or any other affective disorder. And while the specification describes one particular gene rearrangement in a single subject, the methods encompass the detection of any mutation in the GRIK4 gene, where it is not clearly established what structural elements (e.g. how many nucleotides must be deleted from what portion of

the gene) of any detected mutation have the required functional properties (e.g. indicative of schizophrenia). And while Applicants argue that the skilled artisan would recognize the functional consequences of the gene rearrangement described in the instant specification, the issue in the claimed methods is not that the skilled artisan would recognize that a large gene deletion may affect expression of that gene. The methods require that the skilled artisan would be able to correlate some amount of detected mRNA or protein with the susceptibility phenotype. However such methods are not taught in the specification or known in the prior art; For example is the detection of an mRNA level that is 0.5 times, or 0.85 time, or 0.95 times that of the average found in a non-schizophrenic patient in fact indicative of a susceptibility? And how much protein need be detected in any particular sample tissue to establish that a subject is in fact susceptible to any different affective disorder?

Applicants have pointed (p.17 of Remarks) out that there is no legal requirement for enablement that a particular degree of statistical significance be demonstrated. The Examiner recognizes this point, but maintains that, as set forth in the rejection, the statistical analysis of associations in any population to determine a p-value of less than 0.05 is typically considered significant in the scientific community, and that such a p-value can be evidence of the robust and reliable nature of a relationship. In the is no such analysis.

Finally, while Applicants argue that the amount of experimentation required to practice the claimed methods would not be undue (p.17-18 of Remarks), the Examiner maintains that the practice of the claimed method requires knowledge of a correlative

association between any of several different detected analytes (e.g.: any GRIK4 nucleotide mutation, any mRNA level, any protein level) and phenotype susceptibility, where have to perform experimentation to actually determine if such a relationship exists would be undue in the practice of the claimed method.

The rejection as set forth is **MAINTAINED**.

Withdrawn Claim Rejections - 35 USC § 102

9. The rejections of claims under 35 USC 102 as anticipated by the prior art are **WITHDRAWN** in light of the amendments to the claims to require determination of a mutation wherein the determination identifies a subject as having susceptibility to schizophrenia and/or affective disorder.

Conclusion

10. No claim is allowable.

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from

either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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